REVIEW ARTICLE

Recent Technological Advancements in Multiparticulate Formulations: The Smart Drug Delivery Systems

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Abstract

Pharmaceutical research is achieving and focusing new goals in the field of delivery systems, which are helpful to aggravate therapeutic objectives while alleviating side effects. As per current reviews, it has been critiqued that multiparticulate (MP) specifically with low-risk of dose dumping formulations will be much more suitable in context to achieve controlled and delayed release profile. These systems have received the great attention of pharmaceutical industry as they deliver an accurate amount of drug at the right time and location thus increasing patient compliance and economic feasibility. Despite recent advancements in MP drug delivery systems, further exploration of this technology is need of the hour to find out a solution to many of the dose/release/drug combination efficacy related problems. Present review comprehensively summarizes various aspects related to development and features of recently developed MP dosage forms and recent industrial advancements by extensively literature search on various scientific databases, Google, and websites of various associated pharmaceutical industries and patenting authorities across the world. MP system consists of pellets, granules, beads, microspheres, mini/micro tablets filled into sachets, capsules, or compressed into tablets. In comparison to single traditional dosage form, in the MP system dosage forms of the drug has been divided among various discrete delivery entities. Besides this, these are preferred due to their comparatively greater dispersibility in gastrointestinal tract, increased bioavailability, reduced-risk of systemic toxicity, decreased dosing frequency, increased patient compliance, lesser variability in concern to absorption, reduced chances of dose dumping, and accurate dosing. This article mainly emphasizes on technical intricacies and further possible exploration of these smart formulations for versatile pharmacotherapeutic benefits.

Key words: Capsules, multiparticulate drug technologies, multiple unit dosage forms, pulsatile drug delivery, tablets

INTRODUCTION

Oral modified drug delivery system (DDS) has two various well-known broad classes which are named as single unit dosage forms (SUDFs) and multiple unit dosage forms (MUDFs). If various mini-tablets will be filled into hard capsules or compressed into tablets of bigger size, these can be released as multiple dosage forms as subunits, whenever disintegrated. The concept of MUDFs was originated in 1950s and this particular concept can also be known as multiparticulate (MP) DDS. After gaining much of the popularity, the production of MP dosage forms became a common strategy for controlling the release of the drug. This has been evidenced by consistent and reproducible release pattern in comparison to SUDFs. The production of mini-matrices has grabbed attention in the 1990s and is supposed to be the most promising area in pharmaceutical research in context to a controlled pattern of drug release and the possibility of dose adjustment.[1] MP modified release DDS are considered to be much more advantageous in contrast to SUDFs because of enhanced bioavailability, less risk of toxicity gastric irritation, and predictable emptying. Whenever, MP units are ingested, initially these are released in the stomach and afterward these will be transited to the small intestine and

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finally reached to the gastrointestinal tract (GIT) which leads to uniform release of drug with lesser mucosal irritation.[2,3]

Keeping all the excellence of MP formulation in view, present article has been compiled to particularly highlight various aspects related to MP dosage forms like its types, mechanisms associated, industrial technologies and products, etc. Most of these technologies are developed by industries for specific purposes and has an excellent scope for future research as much of the related work is still not reported until date. Furthermore, this paper will provide a clear understanding of multifaceted issues regarding MP based smart DDS, which may open a new vista in dosage form development.

Mechanism of drug release from MPs various mechanisms involved in drug release from MP delivery system are given below:

DIFFUSION

There are two different methods by which diffusion controlled release can be obtained and that includes: monolithic and reservoir devices (membrane controlled devices). In monothilic devices, drug products are tend to disperse in a matrix, and diffusion based drug release is observed. The diffusion may take place either through porous ceramic (or polymer) matrix, or, by passing between polymer chains on a molecular level. In contrast to above said devices, reservoir device is the example in which drug is available as a core or encapsulated within polymer film.

In this method, drug or solvent moves across the sides through a membrane filter. In this device, the diffusion rate of molecules is determined by the membrane filter, drug permeability, solvent as well as the geometry of the device. In both the devices, for the valid boundary conditions, the release characteristics of reservoir is characterized by Fick's second law, where drug flow is based mechanistically on a solvent diffusion.[4]

OSMOSIS

Osmotically controlled DDS (CDDS) based devices are supposed to be the most consistent CDDS especially for drug delivery through oral route. To have a check on drug release in a controlled manner, osmotic pressure can be used as a driving force. These systems generally consist of osmotic agents such as semipermeable membrane, excipients, and drug.[5]

EROSION

In some of the cases, wherever coatings are specifically designed to wear away gradually with time, and hence these type of drugs which are contained within the particle can be delivered by erosion.

ADVANTAGES OF MPS

These are multifarious benefits which include its predictability, reproducibility and have short gastric time. Apart from this improved bioavailability, stability and tolerability, less inter- and intra-subject variability, lesser number of adverse effects, ease of mixing pellets with different composition or pattern of drug release, no risk of dose dumping, improved medication adherence and patient compliance, possibility to get a unique release profile and its ability of commercialization, intellectual property right protection for globalization of developed product make it much more advantageous.

LIMITATIONS OF MPS

There are some limitations which include various different parameters like these have low drug loading capability, comparatively greater requirement of, process variables in contrast to others, the involvement of a large number of formulation steps, economically more costly in context to production. Apart from this, it demands advanced technology as well as trained/skilled personals for manufacturing.

TYPES OF MP SYSTEMS

Pulsatile release by rupturing of membrane

In this particular system, a coating of drug is to be done on sugar beads coated with insoluble as well as a swellable topmost layer. Superdisintegrants like carboxy methyl cellulose, sodium starch glycollate are added as swelling agents. Contact of these systems with water causes swelling of coating which results in rupture and drug is finally released. This release is pH independent.[6] Coating thickness usually defines the lag time depending on varying concentration of plasticizers.

Pulsatile release by osmotic rupture of membrane

This type of MPs consists a core which includes drug molecule, disintegrating agent, and lipid. Usually, on imbibitions in an aqueous medium, water penetrates inside the core coated with centralized admission policy and result in the displacement of inner lipid material.[7] This results in the generation of critical stress, which ultimately results in rupturing of coating and drug release.

MP BASED TECHNOLOGIES

Capsule-in-a-capsule technology

Multispectrum of therapeutic applications can be attained by using single oral capsule dosage form based on

capsule-in-a-capsule technology as shown in Figure 1a. In this, it is also possible to insert a prefilled capsule of smaller size into a liquid filled capsule of larger size.[8] Coated or uncoated gelatin or hydroxypropylmethylcellulose (HPMC) may be used to develop such formulations. To attain multiple release profiles, immediate and sustained/controlled release formulations may be filled in outer larger and inner smaller capsules respectively. In addition to modifying release profiles, with appropriate coating, inner and outer capsules can target diverse regions of the GIT (small intestine or colon). Different active pharmaceutical ingredients (APIs) for combination therapy or having incompatibilities may also be administered in different compartments of this formulation. Formulations with different physical properties and consistencies like liquid, semi-solid or powder may also be suitably given to patients receiving multiple therapies.

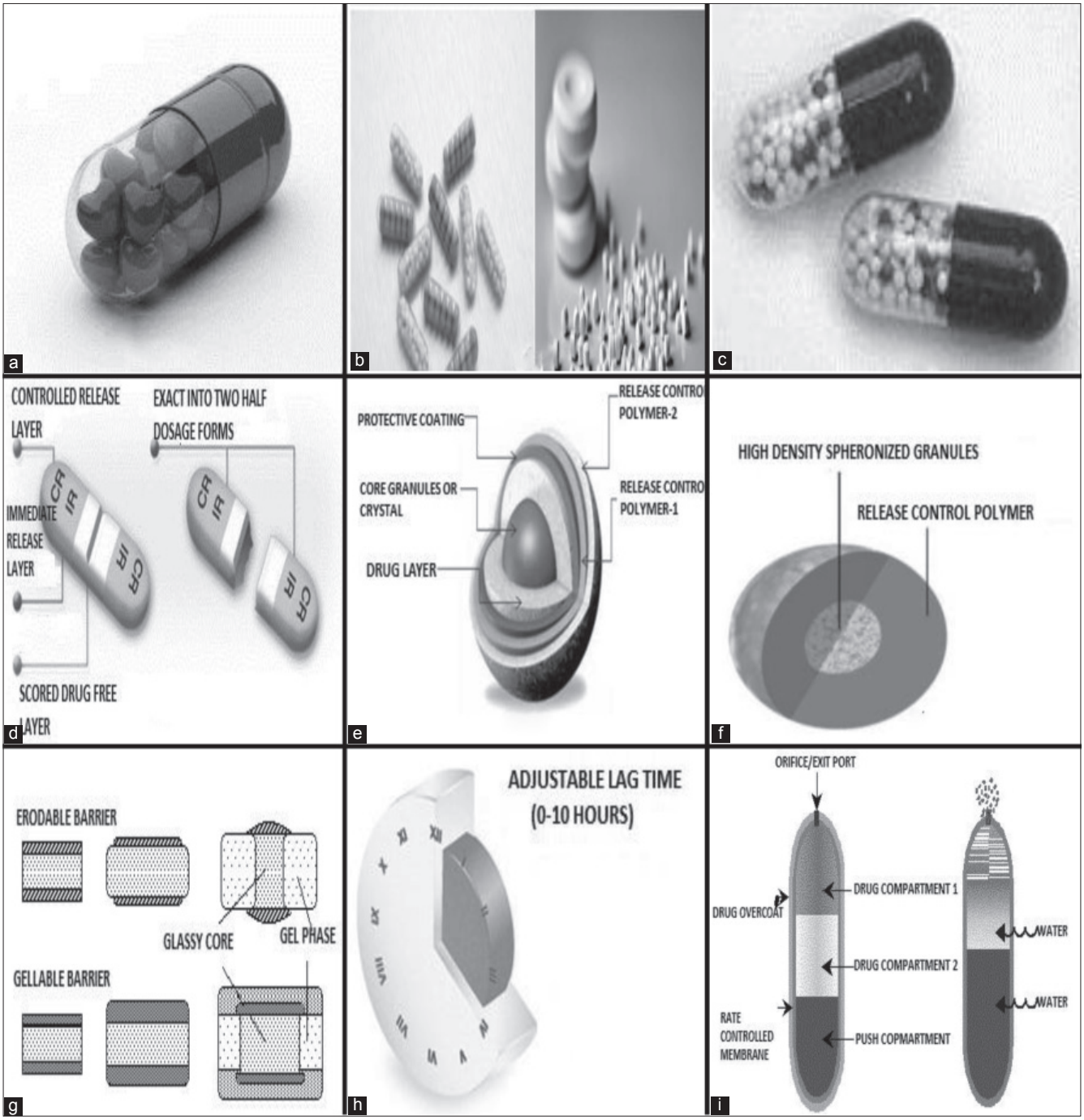

Figure 1: Representative diagrams of smart drug delivery systems - I: (a) Capsule-in-a-capsule technology; (b) Mini-tablets delivered as a (a) tablet or (b) capsule; (c) programmable oral drug absorption system technology; (d) ACCU-T tablet; (e) Spheroidal oral drug absorption system technology; (f) Orbexa technology; (g) Geomatrix technology using hydrophilic polymer; (h) Geoclock technology; (i) OROS technology

This formulation is also suitable for nutraceuticals as well as pharmaceuticals having a simplified drug regimen. Various advantages of Capsule-in-a-capsule technology are as follows:

- This technology is helpful to provide controlled as well as multi-phase release for single and combination dose regimen even for over the counter drugs.
- Two independent compartments are comprised in one single oral dosage unit.
- By taking it into consideration, patient convenience and compliance and cost effectiveness can be overruled.
- Delivery of various incompatible APIs is possible.
- In addition to all above, sustained, pulsed or delayed release profiles can be obtained.

Tablets-in-a-capsule technology

Coated pellets are another category of solid oral dosage form that exhibits therapeutic outcomes in the form of controlled release capsules.[9] A new approach that comes into existence consists of combination of features of both modified and controlled release tablets in one dosage form.

Usually, drugs are encapsulated by either biodegradable or erodible polymer within a barrier material by one or other method. A wide variety of lag times can be obtained in release profile only by varying the thickness and structure of barrier material concentrating on the barrier material structure and thickness.[10] Erosion or degradation of inner reservoir core results in rapid release of drug incorporated. By filling versatile tablets in a hard capsule, multifunctional and multiple unit systems with various lag times for oral use, for e.g., Rapid-release mini-tablets, sustained-release mini-tablets (SMTs), pulsatile mini-tablets, and delayed-onset SMTs can be developed by filling versatile tablets in a hard capsule, by using various combinations of mini-tablets, multiple pulsatile DDS, site-specific DDS, slow/quick DDS, quick/slow DDS, and zero-order DDS could be formulated easily. Production of mini-matrices using tablet punching technology is another attractive alternative for the production of pellets as it will lead to high production yields and the presence of solvents (e.g. water) can be avoided. Various drug entities can be formulated in SUDF as MP based dosage form enabling them to GIT at the same or variant site in combined manner including two or more incompatible drugs.[11] The combination of MPs, i.e., same drug molecule in a single dosage and even pellets of different release rates of the form are also permitted in this system. In contrast, to this these greater surface area-to-volume ratio of these formulations also provide desired shape for the application of film coatings. The preparation process of MPs necessitates extra care and fine adjustments of various equipment like tableting machines for the preparation of mini-tablets. Because of lower bulk densities of pellets compared with compressed tablets the volume a dose is usually higher than for tablets whereas in comparison to larger SUDFs, the specific surface area a dose of multiple units is higher and more coating material is necessary to obtain coatings of the same thickness for controlled release.[3] Mini-tablets are those which tend to have a diameter equal to or smaller than 2-3 mm. Like other MUDFs, various mini- tablets can be either filled into hard capsules or compacted into bigger tablets that, after disintegration, release these subunits as multiple dosage forms are shown in Figure 1b. Mini-tablets are better alternatives for granules and pellets because of their relatively easy manufacturing process, suitability for coating to achieve sustained pattern of drug release. The development of mini-tablets for controlled drug release seems to have a vital focus of research into oral dosage forms due to their added benefits like smaller size in comparison to dosage forms containing granules and pellets.

Advantages associated with mini-tablets are given below:

- Relatively easy manufacturing
- Due to its excellent size uniformity, regular shape, and smooth surface.
- Offer of easily coatable substrate with polymeric membranes for modified release purposes
- It combines the advantages of MUDFs with the established techniques in tablet manufacturing and lesser limitations as compared to extrusion/spheronization
- Mini-tablets also offer an alternative as dosage forms of equal dimensions and weight with the smooth regular surface can be produced reproducibly and constantly
- It has low-risk of dose dumping, less inter- and intra-subject variability, high degree of dispersibility in GIT thus minimizing the risks of high local drug concentrations. The concept of tablet in capsule technology is characterized by various facts. The real fact holding the truth behind the dose is that it can be administered as a multiple unit dose, each one contains metered dose of drug, which is considered to be combination of the quantity of the drug in each subunit as well as functionality of the entire dose whose effect is directly proportional to the functionality of unit dose.[12]

Tablets-in-a-capsule technology offers wide variety of benefits. Some of them are given below:

- Lowered treatment failure rate and lower case-fatality ratios have increased significant saving
- Mutually controlled and multi-phase release profile could be attained for both unit or combined prescription as well over the counter dosages
- Cost effective as well patient compliance therapy could be targeted with patient convenience
- Promising delivery of incompatible APIs. Multiple release profile could be attained as sustained, pulsed or delayed
- Drug delivery can target two different regions of GIT.

RECENT MP BASED INDUSTRIAL ADVANCEMENTS

Programmable oral drug absorption system (PRODAS)

This expertise offered a number of controlled-release mini-tablets in a hard gelatin capsule which is a means of distinctive and combined advantageous delivery system of tablet and capsule as shown in Figure 1c. PRODAS tool is believed to equally signify MP and hydrophilic matrix tablet technology and thus could provide all the related benefits of both DDS in single dosage form. Normally size ranges from 1.5 to 4 mm (in diameter) in controlled-release mini-tablets. Single dosage form can be designed of desirable characteristics by using mini-tablets with different release rates can be combined and formed to give the desired release rates. These combinations could be of different types, i.e. it may be immediate-release, delayed-release, and/or controlled-release mini-tablets and show the distinctiveness of a number of different conventional dosage forms.[13]

Usually, immediate release, sustained release and delayed release component will ensure fast acting, controlled release/ protection and site/regional release and food resistance, respectively.

As per to the formulation, PRODAS includes manufacturing of mini-tablets by direct compression of an immediate release granulate that contain active ingredients. Afterward, these mini tablets are forwarded into hard gels and capsules, which result into the final dosage form. Another area includes manufacturing of controlled release formulations where this technique is valuable used. Release rate of drugs from every individual mini tablets can be modified by adding various polymer combinations within granulates.

Consequently, mini tablets could be coated with polymer solutions which would offer supplementary delayed release profile. This coating technique is accommodated as an essential tool especially in for highly water soluble or gastro irritation causing drugs, where drug release can be delayed until the formulation reaches more distal regions of the GIT.

PRODAS expertise holds significance in the intrinsic flexibility to the formulation, whereby combinations of mini tablets, each of which is with different release rates, are included into a single dosage form. In addition to potentially permitting controlled absorption over a specific period, this also may permit targeted delivery of drug to particular sites of absorption throughout the GIT.[14]

ACCU-BREAK

ACCU-BREAK tablet technology focuses on the use of an inactive layer (segment) as the break region. Split tablets of unequal size will provide the same dose, as breaking is to be done in the inactive segment. Efficient dose adjustment without a new prescription may be allowed by ACCU-BREAK. In bilayer (ACCU-B) tablets, the layer containing drug could be eroded as multiple equal segments, all adjacent to an inactive breakable support segment. Thus, a tablet could be broken easily into the specific dose desired.[15] ACCU-B tablets can be made to split into as many as four segments of equal doses me so that dose titration either up or down can be accomplished easily without issuing a new prescription. ACCU-T tablets can be split into two tablets, each of which contains the precisely equal amount of active drug. Figure 1d shows the ACCU-T tablet, in which tablet contains drug layers at the "top" sides, and a scored, drug-free layer (off-white) in the middle that serves as a break region if a half tablet is desired.[16] ACCU-BREAK technology should permit reductions in cost to patients both by using half doses of larger tablets and by having fewer co-pays. In addition, it may also promote adherence to therapy by reducing the need to fill new prescriptions could also investigate he effect on adherence to therapy as a result of using a half tablet for necessary dose decreases rather than having to issue and fill a new prescription.

Spheroidal oral drug absorption system (SODAS)

SODAS are beads of 1-2 mm in diameter, having controlled release pattern produced by MP technique as shown in Figure 1e. The drug in a bead is embedded in internal inert core consisting of multiple layers of polymers with other excipients so as to have controlled release of the drug.[17] These beads performs release by a diffusion mechanism. Polymer dissolves in GIT which lead to formation of pores in the outer membrane of the bead which are gateway for fluid entery into the bead to dissolve the drug. The solution of drug formed inside the beads diffuses in a controlled manner causing prolonged absorption. Excipients used for the various purposes like to ensure optimal stability and solubility may also influence abrupt environment of the drug within the inert core. To pack these SODAS capsule or compressed tablet could be used to give final dosage form. These capsules can also be used for uncooperative patients for traditional dosage in a different way by opening the capsule and sprinkling the beads on soft food.[18]

Programed multiple-action delivery system (PMDS)

In contrast to particularly controlled release technologies, PMDS technology could be helpful to provide for the multiphasic delivery of any active ingredient and hence designed accordingly for delivery in a more controlled fashion, so that release of the active ingredient can be achieved at predetermined time intervals and their appropriate levels on a consistent basis. Apart from this, it also alleviates technical challenges while developing MP dosage forms, i.e. achieving passable uniformity and duplicability of a product with a

variety of release rates. Other than this, this technology has various benefits which comprise enhanced dosing flexibility that modifies product efficacy in a positive manner and reduced side effects.[19]

Orbexa

Orbexa technology is another technology in which high drug loading is one of the possibility, and it is particularly best suited for those products which ultimately needs granulation. By using this technology, controlled sized and bearable beads along with a defined-based granulation extrusion with specified density can be manufactured along with spheronization techniques given in Figure 1f. For additional release rate control, the release rate controlling membranes can be used to coat resultant beads, and these can be filled into capsules or provided in sachet form.[20] In comparison to the other systems, this process is supposed to be unique because it permits for higher drug loading, therefore, process is believed to be flexible and suitable for enzymes or other sensitive materials.

Eurand's Orbexa technology can find its way in following areas which includes:
- Gastroprotection
- Delayed release
- Sustained release
- Site-specific delivery
- Pulsatile delivery
- Complex release patterns
- Separation of incompatibles
- Combination products.

Advantages of Orbexa are:
- Possibility of aqueous or solvent-based granulation
- Sensitive molecules like proteins can be processed with high-speed
- Holds suitability for high drug loading.

Time multiple action delivery systems (TMDS)

The TMDS is a technology to control release rate in a planned manner of multi-excipient within a single tablet over an extended period of time.[21]

Geomatrix

Geomatrix is considered as deep-rooted, validated and customizable multi layered oral drug delivery platform technology given in Figure 1g, as it is highly vibrant and is applicable to broad range of drugs to attain multiple release profiles. Manufacturing is comparatively easy by using well-established ingredients and conventional production equipment. Modulation of drug release profile in case of multi-layered tablets could be performed by targeting two key parameters:
- Use of highly swellable hydrophilic polymers (e.g. HPMC)
- Dynamic control of the surface of the layer containing the drug that is exposed to surrounding fluids.

The drug release rate within the body is controlled by different rates of swelling, gelling, and erosion as well as the combination of layers. Geomatrix system is helpful because when the patient will swallow the drug this system can control quantity of drug released by controlling surface of the drug-containing layer exposed to fluids. Afterward, with time, due to swelling in the core there is increase in the surface area, and hence it help to accommodate the decrease in drug concentration. Geomatrix system can be characterized by its highly pliable and reproducible nature toward required release properties of drugs.[22]

Various benefits of Geomatrix based systems are as given below:
- Different and wide variety of release profiles can be exploited by using this highly versatile platform.

Applications of Geomatrix include:
- A broadened range of release profiles
- Controlled release of every category of soluble drugs
- Zero order and bi-phasic release of drugs either rapid then slow or ascending profiles
- Release of two or more drugs at different rates
- Simultaneous or phased release of several drugs at individualized release rates from a single tablet.

Geoclock

Geoclock, a known oral drug delivery technology, which is independent on food or pH and which can be a suitable option to be used to release the drug from the tablet after a pre-defined and desired lag-time. Geoclock can be used for delivery of one or more drugs with different pulses as per already defined time intervals between these pulses, or to focus on the colonic release of drugs. Geoclock is given in Figure 1h. The delivery profile may be varied for each and every API wherever more than one drug is included. Geoclock minimize the need for capital investment as its manufacturing is easy by using conventional production equipment.[23]

Geoclock constitutes a dry-coated tablet which includes an active drug core inside in the tablet whereas its outer covering consists of combination of hydrophobic wax and fragile material. Before releasing the active drug, this particular can generate a pH-independent lag-time. The active drug will be released either as a burst out or as a defined and controlled pattern after its pre-defined and configurable lag-time. The controlled release characteristics of the inner core are modifiable for achieving the desired profile. Geoclock can be helpful to target location independent drug delivery in the GIT, pH or food, i.e. chronotherapy-focused.

Examples of the application of Geoclock include:

- A burst release after a long lag-time or a slow release rate after a short lag-time.
- Specific drug delivery at the colonic level, which is valuable for drugs targeted for colonic absorption.
- Multiple pulse release, e.g. to mimic multiple daily dosing of conventional formulations.[24]

Geoclock is an approved technology that has found its way in US and Europe markets. Tablets can be prepared by using standard tableting machine, at low capital investment.

Intelli matrix

This technology consists of specific blend composition of various polymers such as hydroxyethylcellulose, and enables precise profile control and site-specific drug delivery. The drug will be released at predetermined rates depending on the constituents of the blend and the manner in which this interact, the use of the blend with a drug, while taking care of protective characteristics to both the drug and the GIT. This technique is most applicable for those drugs which require precisely controlled first order release profiles, i.e. where the amount released with time is dependent on one component like the amount of drug available for dissolution.[25]

COLAL

COLAL constitutes specific type of a coating which is composed of ethyl cellulose and one another form of starch called "glassy amylose" for drug pellets, tablets or capsules. The specificity of glassy amylose lies in its unique potential of not getting digested by human enzymes, whenever it moves down the GIT, it get digested by bacterial enzymes which are present only in the colon. When the coated product reaches to the colon, the coating is degraded and hence the drug is released on its target.[26,27]

COVERA-HS

Covera-HS is an advanced tablet coating technology which also holds modern DDS which ultimately mimic the body's typical 24 h circadian variations in blood pressure and heart rate. By using this particular technique, first once-daily formulation of antihypertensive/anti-anginal agents came into picture. This distinctive character of delivery technology is known as COER-24TM (Controlled-Onset-Extended-Release) which was developed in synchrony with Alza Corp. Nowadays Covera-HS technology has produced a controlled-release verapamil formulation, which has been approved for the management of both hypertension (high blood pressure) and angina pectoris. Covera-HS has been designed for oral dosage form which can be given at bedtime[28] hence its most crucial, i.e. the peak concentration of the drug will be delivered in the early waking hours when the risk of blood pressure, and heart rate is at their highest risk. Hence by using this technique, there will be minimal drug delivery during sleep when blood pressure and heart rate are considered to be at lowest.

Dividable multiple action delivery system (DMDS)

This technology has considerable dosing flexibility that is supposed to upgrade product efficacy and minimize side effects and hence specially designed to serve the similar purposes. Once traditional controlled release tablet is broken, it usually lose its controlled release mechanism of delivery. DMDS technology is always helpful to achieve exactly the same release profile on each respective portion of the tablet whenever broken down in two equal parts will as the whole tablet is getting.[29] Furthermore, this technology allows the adjustment of the dosing requirements as per the clinical needs of patient and physician without weakening the efficacy of the tablet.

Egalet

Egalet time release system has three main components which includes:

1. A coat
2. A drug release matrix
3. A lag component.

The middle portion, i.e. inner layer of matrix is generally composed of the drug whereas outer layer is entitled to provide a predetermined delay in release of the drug g.[30]

Intestinal protective drug absorption system (IPDAS)

IPDAS, MP tablet technology, has been developed with special prominence which will be able to strengthen the GI acceptability. The drug is released out in the form of the resultant solution in a controlled, predetermined manner whenever fluid enters the core of the beads and dissolves the drug. This allows for prolongation of the *in vivo* dissolution and absorption phases.[31]

In the IPDAS technology, major components are high density controlled release beads, which are compressed into a tablet form. After ingestion of these drugs, these disintegrated at a rapid pace and get dispersed into the beads containing drug molecules which finally enters to the duodenum and are released in the GIT in a controlled and cautious manner, independent of the feeding state. The active ingredient from the MPs is released via diffusion which is a general phenomenon either through the polymeric membrane and or the micro-matrix of polymer/active ingredient formed in the extruded/sprouted MPs. The wide dispersion of irritant drug throughout the GIT has also been ensured by the intestinal protection of IPDAS technology. These capsules can be used by sprinkling it on soft foods which will be helpful for those patients who are unable to swallow this particular dosage form.[32]

OROS technology

This OROS delivery systems was particularly adopted for terribly water soluble drugs. The push-pull system is comprised a bilayer or trilayer tablet core varieties but consisting of one push layer and one or more drugs layers. In this delivery system, the drug layer and the osmotic engine are wrapped in a hard capsule which is further sheathed by the rate controlling semipermeable membrane. Drug layer and osmotic engine are separated with the help of a barrier layer which constitutes an inert substance as Figure 1i. A laser drilling is done at the opposite end of the osmotic engine which provides a delivery orifice is or an outlet for the drug. The drug layer contains the poorly soluble drugs, osmotic agents and a suspending agent. The push layer usually constitutes an osmotic agent and water swellable polymers. The tablet core is surrounded by a semipermeable membrane.[33] The recently developed L-OROS SOFTCAPTM delivery system has combined the attributes of a controlled-release and bioavailability-enhanced delivery system to intensify compliance and therapeutic effect. L-OROSTM technology was developed by Alza to overcome the drug solubility issue.

One step dry coating technology (OSDrC)

OSDrC technology is a technology which allows placement of a variable number of cores of any shape into the tablet which can be placed on different positions wherever they need to be positioned for optimum delivery of APIs. OSDrC meant to be one step dry coating technology. This technology has opened the doors to a new and most awaiting world of pharmaceutical tablet manufacturing with advantages like uniqueness, high quality, low budget and Innovativeness. The OSDrC rotary tableting machine is quite useful as it includes its variable double-punch configuration, which ultimately supports single-step manufacturing of pharmaceutical products as Figure 2a. Apart from the commercial-scale production of conventional cored (tablet-within-a-tablet) tablets, this machine is supposed to be ideal for manufacturing a variety of high-quality drug products at comparatively lesser budget. This innovative technology can also be a substitute for providing conventional sugar- and film-coated tablets.[34] This technology also has allowed production scientist to formulate a novel dosage forms and align capability with scientific creativity.

Programmable oral release technologies (PORT)

It offers multiple programmed release of drug and uses a uniquely coated, encapsulated system. As per the basic design of the Port technology a tablet constitutes polymer core matrix which is further coated with a semipermeable, i.e. acting as rate-controlling polymer. Proprietary solubilization agents are used to coat the drugs which are with poor solubility. This is particularly done to ensure uniform controlled release from the dosage form. Port technology is given as Figure 2b. Port system's basic design of capsule consists of a hard gelatin capsule coated with a semipermeable, rate-controlling polymer. The osmotic energy source which also includes therapeutic agent (to be delivered) in it is on the inner side of the coated capsule.[35] This capsule is generally sealed with a water-insoluble lipid separator plug, along with an immediate release dosage which can be added to complete the dosing options.

TIMERxt

It is hydrogel-based controlled release technology and quite multifaceted. The unique nature of TIMERx is to provide various different release profiles, ranging from zero order to chronotherapeutic release and its intermolecular physical chemistry was described in relation to the technology's potential. As per various evidences, it is evident that the requirement of complex processing or novel excipients is being replaced with "molecular engine" which allows desired drug release profiles so far to be "factory set" by the following a simple formulation development process. This particular technology is basically, focused on mixtures of xanthan and locust bean gums, which are finally mixed with dextrose. These components workout together due to their physical interaction and to form a strong binding gel in the presence of water.[36] The drug release from the GIT into the TIMERxt gum matrix is dependent on the rate of water penetration which is a controlling factor due to which, drug expands to form a gel and subsequently releases the active drug substance. Another examples of other controlled release systems includes erodible polymers in different forms, programmable pulsatile release capsule devices, guar gum-based matrix tablets, sigmoidal release systems and self-exploding micro-particles which find future applications in chronotherapy.

Chronset

OROSs delivery system is a proprietary which is used to release the drug in a time- or site-specific manner to the GIT as bolus drug dose (80% drug release within 15 min). By using Chronset technology, before the release of the drug, the drug formulation is completely shielded from chemical, and enzymatic degradation in the GIT and the release timings of drug release are irrespective of GIT contents.[37] Drug release onset times which may vary from the range of 1-20 h can be achieved by balancing the factors including osmotic engine, the semipermeable membrane, and the other attributes of the system configuration.

Ceform

According to this particular technique, uniformly sized and shaped microspheres of pharmaceutical compounds can be produced. "Melt-spinning," approach is exploited in this technology which particularly involves subjecting of solid feedstock (i.e. biodegradable polymer/bioactive agent combinations) to a variety of factors like temperature, thermal

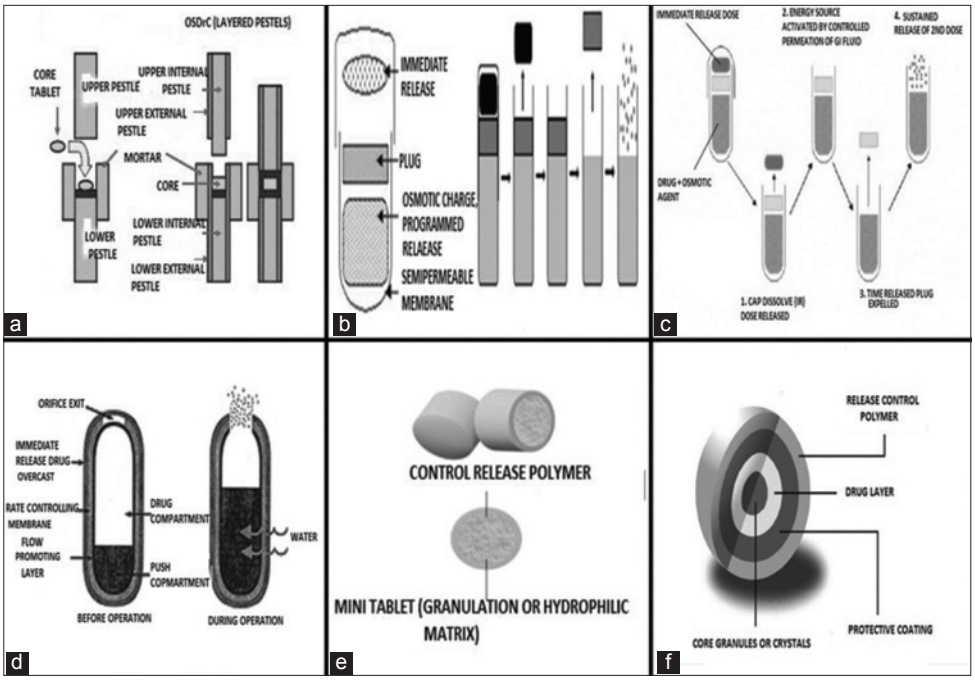

Figure 2: Representative diagrams of smart drug delivery systems - II: (a) One Step Dry Coating Technology; (b) Port technology; (c) SyncroDose technology; (d) Chronotherapeutic Oral Drug Absorption System technology; (e) Eurand minitabs technology; (f) Diffucaps technology

gradients, mechanical forces, flow, and flow rates during processing. The microspheres produced by this method are perfectly spherical in their shapes and has achieved a diameter of 150-180 mm, which also allows high drug content in it. The microspheres can be exploited for a various wide variety of uses which may includes tablets, capsules, suspensions, effervescent tablets, and sachets.[38] The microspheres may be available into fast/slow release combinations by coating them with an enteric coating which will be helpful for the controlled release of the drug.

Pulsincap

The Pulsincap is a system which is made up of a water insoluble capsule body filled with drug formulation. The body of the pulsincap is closed at the open end with a swellable hydrogel plug, and the length of its plug decides its lag time. The plug material is made up of insoluble but permeable and swellable polymers which may include polymethacrylates, as well as erodible compressed polymers in the form of hydroxypropylmethyl cellulose, polyvinyl alcohol, and polyethylene oxide) along with congealed melted polymers which includes saturated polyglycolated glycerides, glyceryl monooleate, and enzymatically controlled erodible polymer, i.e. pectin, agar).[39]

3D printing technology (3DP)

Three-dimensional printing is known to be a rapid prototyping technology and novel solid which is used in the fabrication of complex pharmaceutical oral dosage drug devices. Complicated internal geometries, varying densities, diffusivities, and chemicals can be engineered, but the technique prototyping involves the construction of specific layers which specifically use powder processing and liquid binding materials. 3DP technology has shown its flexibility due to which it can be used in applications linked to linear DDS, colon-targeted delivery systems, oral fast disintegrating delivery systems, floating delivery systems, time-controlled and pulse release delivery systems as well as dosage forms with multi-phase release properties and implantable DDS. In addition to above said advantages, 3DP may also be helpful to resolve the problems related to the delivery of poorly water-soluble drugs, peptides and proteins, highly toxic, potent drugs along with those formulations in which controlled the release of multi-drugs is desired in a single dosage forms.[40] This technology includes the construction of pulsatile tablets in which it involves one continuous enteric excipients phase into which diclofenac sodium was printed into two separated areas and hence samples showed two pulses of release *in vitro* with a lag time between pulses of about 4 h. Later this technology made the basis of the TheriForm's technology. The latter is a micro-fabrication process that works similarly to an "inkjet" printer which is entirely integrated computer-aided development manufacturing process. Products may be before actual implementation of the products preparation process; theses are designed on a computer screen as three-dimensional models.

Magnetic nanocomposite hydrogel

Magnetic nanocomposite is used as remote controlled pulsatile drug delivery due to its temperature responsive

hydrogel. Nanocomposites are manufactured by incorporating superparamagnetic Fe3O4 particles in negative temperature sensitive poly (N-isopropylacrylamide) hydrogels. To produce on demand pulsatile drug release from nanocomposite hydrogel, a high frequency alternating magnetic field was needed to apply. Nanocomposite hydrogel temperature increases above the level of LCTS, which ultimately shows the accelerated collapse of gel.[41] Hence, nanocomposites hydrogel are known to be on-off type of device which controls the drug release and it get on with the help of alternative magnetic field.

SyncroDose

SyncroDose DDS is used to deliver active drug substance at a particular specific site in the GIT or at the optimal time after ingestion, which is referred to as chronotherapeutic delivery. By using this technology, it is possible to deliver drugs after predetermined lag times which will concur with the body's circadian rhythm pattern. It also may allow drugs to be delivered to different sites within the GIT. A SyncroDose tablet includes an inner core which constitutes drug in it and this portion is surrounded by TIMERx -based materials, i.e. compression coating by using gum matrix Figure 2c. With the use of this technology, lag time can be controlled by varying two polysaccharides, i.e. xanthan gum and locust bean gum. Its oral controlled release technologies are already available which can be used for the development and commercialization of products with multiple therapeutic areas.[42]

This technology is specifically helpful in large intestine associated diseases, such as ulcerative colitis, Crohns disease and morning stiffness caused by arthritis. This particular drug is planned to utilize at bedtime, because of its release during the late night hours. This will be helpful because by the time the patient wakes up; morning stiffness has been substantially reduced due to late night release of the drug.

Geminex

Geminex is a dual release technology, which provides the independent release of one or more active ingredients in a single bilayer tablet. The active ingredients release can be determined at different rates which may involve two different controlled release profiles, or a controlled release and an immediate release profile simultaneously.[43] Bi-layer tablet is the basis of this technology which utilizes TIMERx matrix in the controlled release layer or layers.

Chronotherapeutic oral drug absorption system (CODAS)

CODAS is a technique in which drug release is targeted to occur after a prolonged interval. In this technology, a multiparticle system is designed for bedtime drug dosing which is destined to incorporate 4-5 h delay in drug delivery. This delay can be achieved by introducing a level of non-enteric release-controlling polymer applied to drug-loaded beads. The polymer controlling the release pattern of the drug might be a combination of water-soluble and water-insoluble polymers. The CODAS DDS is given as Figure 2d and has empowered a delayed onset of drug release, which may lead to provide more accurately complimenting drug release profile w.r.t circadian patterns. After ingesting these drugs, when the water from the GIT comes closer with the polymer-coated beads, the water-soluble polymer slowly dissolves, and the drug diffuses through the resulting pores in the coating.[44] while diffusion of the drug, its water-insoluble polymer continues to act as a fence, which is helpful to maintain the controlled release of the drug. The rate of release is essentially independent of pH, posture, and food.

PMDS

In comparison to typical controlled release technologies, this technology is designed to provide the multi-phasic delivery of any active ingredient in a more controlled fashion. The active ingredient can be released at predetermined time slots and desired amounts on a consistent basis by using PMDS technology. This technology also has allowed to overwhelm the technical challenges whatsoever are faced at the time of development of MP dosage forms and in achieving acceptable uniformity and reproducibility of a product with an array of release rates.[45] This technology is destined to improve product efficacy by reducing its associated side effects along with enhanced dosing flexibility.

Multi-ingredient multiple-action delivery system (MMDS)

This particular system holds similarity with PMDS, and this system has targeted multiphasic delivery of two or more different active ingredients within a single tablet. MMDS technology is much more controlled and hence more than one active ingredients are allowed to get release from a single tablet in multiple profiles as well as in more controlled fashion.

Concentrated multiple particulate delivery system (CMDS)

As per controlled-release technologies, the release of only one active ingredient one rate of release is targeted. These types of release profiles may not be holding suitability for the drugs of certain therapeutic categories. CMDS technology is designed to control the release rate of multiple active ingredients in a MP dosage form. This technology has overwhelmed uniformity and reproducibility of a pharmaceutical ingredient with a variety of active ingredients specifically for MP dosage forms. Active ingredients are released through an encapsulated form at predetermined time

intervals and desired levels on a consistent basis according to this technology.[46]

Aqualon carboxymethylcellulose (CMC) EZ

Aqualon CMC EZ is the technology in which products are bound to provide ideal performance in dry mixes and in operations with limited mixing/shear capabilities due to their encapsulation. Dispersion is the basic requirement by the hydrocolloids for achieving complete hydration and viscosity. Whenever high shear mixing and dry blending add time are used to target dispersion, it adds complexity to operations which can be prevented by agglomeration and controlling particle size speed of hydration will be lost. Both easy dispersion and fast hydration are offered by Aqualon EZ technology. There are two layers, in the middle layer of the matrix, drug is constituted whereas the outer layers providing a predetermined delay in the release of the drug.[47]

Hypermatrix

Hypermatrix is a novel concept in which hyper-dimensionality is taken into consideration. As per this technology, drug matrix assembly is supposed to be five-dimensional in nature, and hence length, height, width, space, and time are the considered factors. Time-release delivery of a variety of pharmaceuticals can be adjusted by having a good understanding and controllable properties associated with these dimensions facilitates. This hypermatrix technology is the basis of controlled-release drug delivery approach and it works in harmony inside the human body and responding to the multivariate external environment of the GIT, and releasing active drug at the desired time and according to the desired profile.

This can be attained with:

- Spatial recognition and by controlling the optimum GIT site for drug release,
- Defensive control over adverse factors such as food effects or excess acidity
- Temporal control over the time when drug release commences or ends
- Structural control over the physical characteristics of the solid dosage form from ingestion to full release.

Eurand minitabs

The major uniqueness of the Eurand minitabs technology is that it offers the advantages of a tablet combined with those of a MP drug form.[48] Simplicity of tablet formulation is simply combined with the sophisticated drug release control offered by MP drug forms in this particular technology as Figure 2e. The tiny molecules ranging (2 mm × 2 mm in diameter) are cylindrical tablets which constitute gel-forming excipients which ultimately controls drug release rate and in this system, additional membranes may be added to further control release rate.

Eurand minitabs are small sized and these are meant to be filled into capsules as a final dosage form.[49] This may result to form combinational products which will target two or more release profiles within a single capsule. For more accurate dosing, Eurand minitabs offer high drug loading, content uniformity and of course the ability to fine tune release rates for targeted delivery.

Apart from above-mentioned features, Eurand minitabs offer high drug loading, a wide range of release rate designs, and fine tuning of these release rates. The capsules contents can be used as sprinkle when opened.

Diffucaps/Diffutabs

According to this technology, a unit dosage form, one or more populations of drug-containing particles (beads, pellets, granules, etc.) are released into the body specifically in a circadian release fashion. Drug profiles are crafted by layering an active drug component onto a neutral core such as cellulose spheres and furthermore one or more than one rate-controlling, functional membranes can be applied in this system. Customized release profiles and region-specific delivery are being offered by Diffutab technology as given in Figure 2f. In this technology, particular focus is on a blend of waxes and hydrophilic polymers, which are required to control drug release through diffusion and erosion of a matrix tablet.

Diffutabs are found to have their applications in products with high-dose and drugs that require sustained release and particularly for once-a-day dosing. Depending upon the individual needs, the coating materials used could be water soluble, pH dependent or independent or water insoluble. The resultant beads manufactured are usually of small size approximately 1 mm or less in diameter. Different type of release profiles can be targeted just by incorporating beads of differing drug release profiles into hard gelatin capsules. Depending upon the specific requirements, it is possible to constitute any combination, i.e. product of sustained release, pulsatile release, and immediate release profiles.[50]

Aqueous or solvent-based drug solutions can be used for the process of drug layering and this might be applicable to both soluble and insoluble products. Diffutabs has found its way for high drug loading, supporting sustained-release and once-a-day dosing, as matrix tablets utilize a combination of water soluble particles and active drug. For preparation of combination therapies, Diffucaps beads of different drugs can be combined to make convenient single dose units.

CONCLUSION

Novel DDS based technologies have attracted significant attention in recent times for their therapeutic advantages and commercial benefits. MP based technologies offer smart

alternative to conventional DDS especially for patients suffering from chronic ailments like arthritis, asthma, hypertension, etc. due to accurate and timely dose delivery and by reducing the cost, frequency of administration, better bioavailability, and possibility of delivering of incompatible APIs resulting in improved patient compliance. Therefore, these smart DDS present a new vista in the development of patient-oriented drug administration with overcoming the disadvantages associated with presently used conventional dosage forms. Scientists involved in this area may explore potential of these DDS in future for the development of therapeutically advantageous dosage forms. However technical intricacies involved in manufacturing, lack of reproducibility still limit the number of marketed products of these kinds. These hurdles may be overcome by technological advancement and better formulation design in near future. These smart DDS offer prolonged multiple release profiles and hence can be successfully used in chronotherapy. Development of these technologies has opened a new vista in drug delivery approaches and are very prospective candidates of next generation smart delivery systems having tremendous potential of commercial success.

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